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The 2017 Focused Update of the Guidelines of the Taiwan Society of Cardiology (TSOC) and the Taiwan Hypertension Society (THS) for the Management of Hypertension

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Hypertension (HT) is the most important risk factor for cardiovascular diseases. Over the past 25 years, the number of individuals with hypertension and the estimated associated deaths has increased substantially. There have been great debates in the past few years on the blood pressure (BP) targets. The 2013 European Society of Hypertension and European Society of Cardiology HT guidelines suggested a unified systolic BP target of 140 mmHg for both high-risk and low-risk patients. The 2014 Joint National Committee report further raised the systolic BP targets to 150 mmHg for those aged ≥ 60 years, including patients with stroke or coronary heart disease, and raised the systolic BP target to 140 mmHg for diabetes. Instead, the 2015 Hypertension Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society suggested more aggressive BP targets of < 130/80 mmHg for patients with diabetes, coronary heart disease, chronic kidney disease with proteinuria, and atrial fibrillation patients on antithrombotic therapy. Based on the main findings from the Systolic Blood Pressure Intervention Trial (SPRINT) and several recent meta-analyses, the HT committee members of the Taiwan Society of Cardiology and the Taiwan Hypertension Society convened and finalized the revised BP targets for management of HT. We suggested a new systolic BP target to < 120 mmHg for patients with coronary heart disease, chronic kidney disease with an eGFR of 20-60 ml/min/1.73 m^2, and elderly patients aged ≥ 75 years, using unattended automated office BP measurement. When traditional office BP measurement is applied, we suggested BP target of < 140/90 mmHg for elderly patients with an age ≥ 75 years. Other BP targets with traditional office BP measurement remain unchanged. With these more aggressive BP targets, it is foreseeable that the cardiovascular events will decrease substantially in Taiwan.

Key Words: Guidelines • Hypertension • Taiwan Hypertension Society • Taiwan Society of Cardiology

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INTRODUCTION

Hypertension is the number one killer in the world. About 10 million people per year die from causes related to hypertension, and elevated blood pressure (BP) is the most important modifiable risk factor for cardiovascular (CV) diseases.[1] In a recent report from 8.69 million participants in 154 countries,[2] it is estimated that between 1990 and 2015 the rate of systolic BP (SBP) of at least 110 to 115 mmHg increased from 73,119 to 81,373 per 100,000 persons, and SBP of 140 mmHg or higher increased from 17,307 to 20,526 per 100,000 persons. The estimated rate of annual deaths associated with SBP of at least 110 to 115 mmHg increased from 135.6 to 145.2 per 100,000 persons, and for SBP of 140 mmHg or higher increased from 97.9 to 106.3 per 100,000 persons. Projections based on this sample suggested that in 2015, an estimated 3.5 billion adults had SBP of at least 110 to 115 mmHg and 874 million adults had SBP of 140 mmHg or higher.[2] Controlling BP is especially important in Asia, for Asians having higher stroke rate compared to other parts of the world, and SBP is the most important risk factor for stroke.[3]

The BP targets for controlling hypertension are under great debate in recent decade. The reason for this is that we have only a few target-driven randomized clinical trials (RCTs) to test one BP target versus the other. In fact, before the Systolic Blood Pressure Intervention Trial (SPRINT),[4] we have only 2 large-scaled RCTs testing different BP targets, namely the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial for SBP targets in diabetic patients, and the Hypertension Optimal Treatment (HOT) study testing different diastolic BP (DBP) targets for more general patients. Other small studies did not have enough power to test the superiority of one target over the other.[5,6]

Under no confirming RCT to support the optimal SBP targets, the 2013 European Society of Hypertension and European Society of Cardiology (ESH/ESC) HT guidelines suggested a unified SBP target of 140 mmHg for both high risk and low risk patients, a loosening from previous 130 mmHg for high risk patients.[7] The 2014 Joint National Committee (JNC) report further raised the SBP targets to 150 mmHg for those aged ≥ 60 years, including patients with stroke or coronary heart disease (CHD), and raised the SBP target to 140 mmHg for diabetes.[8] There was a discrepancy in the panel meeting for the 2014 JNC report, and 5 out of the 17 panel members actually disagreed with the decision to raise SBP targets.[9] The decision of the 2014 JNC report created tremendous concern.[10-12] Even the American Society of Hypertension (ASH) HT guidelines did not follow the 2014 JNC report.[13]

THE SPRINT TRIAL

The SPRINT trial was funded by National Institute of Health (NIH) of US.[4] A total of 9,361 persons, aged ≥ 50 years, with a SBP of 130 mmHg or higher and an increased CV risk were randomized to intensive treatment group (SBP < 120 mmHg) or a standard treatment group (SBP < 140 mmHg). Four groups of patients were included: 1) clinical or subclinical CV diseaseother than stroke; 2) chronic kidney disease (CKD), excluding polycystic kidney disease, with an estimated glomerular filtration rate (eGFR) of 20 to less than 60 ml/min/1.73 m^2, calculated with the use of the four-variable Modification of Diet in Renal Disease equation; 3) a 10-year risk of CV disease of 15% or greater on the basis of the Framingham risk score; 4) an age of 75 years or older. Patients with diabetes mellitus or prior stroke were excluded. The primary composite outcome was myocardial infarction (MI), other acute coronary syndromes, stroke, heart failure (HF), or death from CV causes.

The unattended automated office BP (AOBP) (Table 1) was used for the measurement of BP in the SPRINT trial.[4] At 1 year, the mean SBP was 121.4 mmHg in the intensive treatment group and 136.2 mmHg in the standard-treatment group. After a median follow-up of 3.26 years, the trial was prematurely terminated owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group [1.65% per year vs. 2.19% per year; hazard ratio (HR) 0.75; 95% confidence interval (CI), 0.64 to 0.89; p < 0.001]. All-cause mortality

Table 1. Four essential elements of AOBP (EMAU)

E	**E**lectronic and automated device
M	**M**ultiple readings
A	**A**veraged mean
U	**U**nattended and **u**ndisturbed spaces

was also significantly lower in the intensive treatment group (HR 0.73; 95% CI, 0.60 to 0.90; p = 0.003). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive treatment group than in the standard-treatment group. The results of the SPRINT trial supported the concept of "lower is better". The impact of SPRINT trial on the management of HT is foreseeable, and the BP targets in the future HT guidelines should be modified accordingly.

RATIONALE FOR MODIFICATION OF BP TARGETS

Based on the main findings from the SPRINT trial and several recent meta-analyses,[14-16] the HT committee members of the Taiwan Society of Cardiology (TSOC) and the Taiwan Hypertension Society (THS) convened and finalized the revised BP targets for management of HT.

The unattended AOBP (Table 1) was used for the measurement of BP in the SPRINT trial.[4] Considering that not all outpatient clinics in Taiwan can provide the complete settings for AOBP, we provided 2 sets of BP targets (Table 2, Table 3). For those who can provide unattended AOBP measurement, BP targets shown in Table 2 are recommended. For those who can only provide traditional office BP measurement, BP targets shown in Table 3 are recommended.

AOBP

The term AOBP refers to BP measurements obtained using a fully automated electronic sphygmomanometer that records multiple BP readings with the patient resting undisturbed in a quiet place without medical staff being present.[17] The use of AOBP can reduce white coat hypertension or white coat effects.[18] Basically, AOBP has 4 essential elements: electronic and automated device, multiple readings, averaged mean, unattended and undisturbed spaces (EMAU) (Table 1).[17] Several devices have been validated to provide accurate AOBP.[18-20] AOBP can be recorded in a variety of locations, including the

Table 2. New BP targets

Categories	Targets (mmHg)	COR	LOE
Primary prevention	< 140/90	I	B
Secondary prevention			
Diabetes	< 130/80	I	B
CHD	< 120/NA^{AOBP}	I	B
Stroke	< 140/90	I	A
CKD	< 120/NA^{AOBP}	I	B
Elderly (age ≥ 75 years)	< 120/NA^{AOBP}	I	B
Patients receiving antithrombotics for stroke prevention	< 130/80	I	B

AOBP, unattended automated office blood pressure measurement; BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; COR, class of recommendation; LOE, level of evidence; NA, not available.

Table 3. Traditional office BP targets

Categories	Targets (mmHg)	COR	LOE
Primary prevention	< 140/90	I	B
Secondary prevention			
Diabetes	< 130/80	I	B
CHD	< 130/80	I	B
Stroke	< 140/90	I	A
CKD	< 140/90	I	A
CKD with proteinuria	< 130/80	IIb	C
Elderly (age ≥ 75 years)	< 140/90	I	B
Patients receiving antithrombotics for stroke prevention	< 130/80	I	B

BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; COR, class of recommendation; LOE, level of evidence.

offices of primary care physicians, hypertension specialists, population surveys, ambulatory BP monitoring (ABPM) units and community pharmacies.[21] The BP readings of the mean AOBP are almost identical to the readings from awake ABPM and home BP monitoring (HBPM), and are about 16/7 mmHg lower than the mean manual BP recorded in routine clinical practice.[21,22]

In a Canadian cohort of 3,627 untreated persons with age over 65 years and a mean follow-up period of 4.9 years, a significant increase in CV risk was seen at a SBP of 135-144 mmHg and at DBP of 80-89 mmHg using AOBP. Therefore, 135/85 mmHg is now defined as the threshold for diagnosis of HT using AOBP,[23] similar to that for ABPM and HBPM.[21] Systolic AOBP correlated with left ventricular mass index, similarly to awake ABPM.[24] AOBP and 24-h ABPM have similar predictive ability for microalbuminuria.[25] The Canadian hypertension guidelines first recommended AOBP for BP measurement in 2011,[26] and AOBP is now the preferred method for BP measurement in office.[27]

There are several different protocols for recording of AOBP.[21] When applying the AOBP targets from the SPRINT trials to clinics, the protocol used in the SPRINT trial should be followed.[4] In the SPRINT trial, AOBP was recorded with Omron HEM-907, with the patients resting alone in an examining room. The protocol included a preset five minute rest period before the device was activated to record three BP readings automatically, at one minute intervals.[21] The mean of the three BP readings was automatically calculated and was shown in the computer of physician's room.

There are comparative studies equating AOBP with ABPM and HBPM.[21] This consensus group suggests that one may use HBPM as an alternative, if AOBP cannot be provided in our busy clinics.

BP TARGETS FOR PRIMARY PREVENTION

Traditional office BP measurement

In our previous 2015 Hypertension Guideline,[28] for patients under age of 80 years and without diabetes, CHD, and proteinuric CKD, BP targets are < 140/90 mmHg. [Class of recommendation (COR) IIa, Level of evidence (LOE) B] The evidence for the SBP target was limited because we do not have any RCT to support this, and the recommendation was mainly based on subgroup analysis or post-hoc analysis of RCTs.[29-32] The findings from the recent Heart Outcomes Prevention Evaluation (HOPE)-3 trial provided additional evidence to support this SBP target.[33] The HOPE-3 trial randomly assigned 12,705 participants at intermediate risk who did not have CV disease to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo. The median follow-up was 5.6 years. The mean BP of the participants at baseline was 138.1/81.9 mmHg; the decrease in BP was 6.0/3.0 mmHg greater in the active-treatment group than in the placebo group. This further lower effect of BP below 140/90 mmHg did not benefit the death from CV causes, nonfatal myocardial infarction, or nonfatal stroke (active vs. placebo group: 4.1% vs. 4.4%, p = 0.40). In one of the three pre-specified subgroups who had a baseline SBP > 143.5 mmHg, the active-treatment resulted in significantly lower rates of the primary outcomes than those in the placebo group; effects were neutral in the middle and lower thirds.[33]

The 10-year CV risk in the HOPE-3 population is 8%,[33] below the inclusion criteria of at least 15% in the SPRINT trial.[4] The traditional BP measuring method, instead of AOBP, was used in the HOPE-3 trial. Therefore, the conclusions from the SPRINT trial can be extrapolated to the population of the HOPE-3 trial. The HOPE-3 is a primary prevention trial and its findings support an office BP target of < 140/90 mmHg for primary prevention. However, the BP target with AOBP for primary prevention is not available at the present time.

Recommendation

- For patients < 75 years of age and without diabetes, CHD, and CKD, BP targets with traditional office BP measurement are < 140/90 mmHg. (COR I, LOE B) (Table 2 and 3)

BP TARGETS FOR DIABETES

Traditional office BP measurement

Diabetic patients were excluded from the SPRINT trial, so we do not have information about the optimal BP targets by AOBP measurement. After the ACCORD

trial, there are many debates regarding the traditional office BP targets for diabetes.[34] There are several drawbacks in the design of the ACCORD trial: 1) patients aged > 80 years were excluded, 2) patients with dyslipidemia were excluded, and 3) patients with serum creatinine > 1.5 mg/dL were excluded.[34] The number of enrollment in the ACCORD trial was too low to have enough power to show difference of intensive (SBP < 120 mmHg) and conventional (SBP < 140 mmHg) strategies in the composite CV endpoints. Despite of this, the annual rates of stroke, a pre-specified secondary outcome, were decreased by 41% (p = 0.01).[35] More importantly, in the standard glycemic control group, the intensive BP treatment group had a lower 5-year CV events compared with the standard BP treatment group (6.9% vs. 9.2%, p < 0.05).[36] In a recent analysis combining the ACCORD trial and the SPRINT trial,[34] the primary CV endpoints, stroke, and HF all favored the intensive treatment group, without significant heterogeneity of the 2 trials.[34]

In a recent meta-analysis comprising 40 trials with a total of 100,354 participants with type 2 diabetes, the effects of BP lowering on all-cause mortality, 4 macrovascular outcomes (CVD, CHD, stroke, and HF), and 3 microvascular outcomes (retinopathy, renal failure, and albuminuria) were examined.[37] Patients with an achieved SBP < 130 mmHg had a 28% reduction in stroke, though CHD and mortality were un-changed. Since stroke is an important CV disease in East Asia, we recommended an SBP target of < 130 mmHg for diabetic patients, using traditional BP measurement.

For the DBP target for diabetes, the HOT trial is the only RCT available.[38] The details of the rationale for choosing a DBP target of < 80 mmHg has been extensively described in our 2015 guidelines,[28] and will not be repeated here.

Recommendation

- For patients with diabetes, BP targets with traditional office BP measurement are < 130/80 mmHg. (COR I, LOE B) (Table 2 and 3)

BP TARGETS FOR CHD

AOBP

The SPRINT trial enrolled 20% of patients with CVD, mostly CHD. The protocol of SPRINT trial defined the clinical CVD as: previous MI, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), carotid endarterectomy, carotid stenting, peripheral artery disease with revascularization, acute coronary syndrome with or without resting electrocardiogram (ECG) change, ECG changes on a graded exercise test, or positive cardiac imaging study, at least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery, abdominal aortic aneurysm ≥ 5 cm with or without repair, coronary artery calcium score ≥ 400 Agatston units within the past 2 years, ankle brachial index ≤ 0.90 within the past 2 years, left ventricular hypertrophy (LVH) by ECG (based on computer reading), echocardiogram or other cardiac imaging procedure report within the past 2 years. It should be addressed that the SPRINT trial excluded subjects with any CV event or procedure (as defined above as clinical CVD for study entry) or hospitalization for unstable angina within last 3 months. Thus, only subjects with clinically stable CVD were included.

The subgroup of CVD in the SPRINT trial comprised 940 subjects in the intensive treatment group and 937 subjects in the standard treatment group. In contrast, subjects without clinical CVD had 3,738 and 3,746 subjects in the corresponding study groups, respectively. As shown in the forest plot for primary endpoints, the relative risk resulting from intensive treatment for CVD subgroup was 0.83 (95% confidence interval 0.62-1.09) compared with standard treatment, which demonstrated a similar trend with that in non-CVD subjects (RR 0.71, 0.57-0.88; p value for interaction 0.39). Likewise, the RRs for total mortality in CVD and non-CVD subgroup were 0.70 (95% CI 0.48-1.02) and 0.75 (95% CI 0.58-0.98), respectively, with a p value for interaction of 0.78. The numbers needed to treat to prevent a primary outcome event and all-cause death during the median 3.26 years of the trial were 55 and 45, respectively. The findings in the CVD subgroups supports the hypothesis that high-risk population benefits similarly or even more from the aggressive BP lowering to a SBP target of 120 mmHg, using AOBP (Table 2).

Recommendation

- For patients with a history of CHD, the AOBP target for SBP is < 120 mmHg. (COR I, LOE B)

Traditional office BP measurement

There has been no target-driven RCT using traditional office BP measurement for patients with CHD. The recommendation for CHD in our previous guidelines is < 130/80 mmHg.[28] This is based on several RCTs testing ACE inhibitors or calcium channel blocker in patients with CHD,[39-41] and also based on meta-analyses.[42-44]

There are 2 important meta-analyses available after our 2015 guidelines. An updated systematic review comprising 19 trials and 44,989 participants demonstrated that intensive BP lowering provided greater vascular protection than standard regimens for major CV events [14% (95% CI 4-22)], MI [13% (0-24)], stroke [22% (10-32)], albuminuria [10% (3-16)], and retinopathy progression.[15] These beneficial effects were consistent across major patient subgroups and types of interventions (all p for heterogeneity greater than 0.05) and significant gains could be achieved from further lowering of SBP to lower than 140 mmHg. Another meta-analysis with 123 studies and 613,815 participants suggested that the relative risk reductions was proportional to the magnitude of BP reductions achieved even with baseline SBP less than 130 mmHg.[14] More importantly, no significant differences existed when trials were stratified by baseline CHD.

Recently, in a large international coronary artery disease registry, intensive BP reduction has also been shown to render more CV protection than the strategy with BP target at 140/90 mmHg.[45] The CLARIFY registry, by enrolling 22,672 hypertensive patients with stable CHD, demonstrated that subjects with SBP 120-129 mmHg and DBP 70-79 mmHg were associated with the lowest risk of the primary endpoints, the composite of CV death, MI, or stroke.[45] This finding supports the BP target < 130/80 mmHg for CHD patients in our 2015 guidelines.[28] Interestingly, a reverse relationship of BP and CV risk was observed, in which SBP of less than 120 mmHg and DBP of less than 70 mmHg were each associated with increased adverse CV outcomes. One should be very careful in interpreting these data because the baseline risk levels were different in each subgroup. Those who achieved a SBP level < 120 mmHg, comparing with those who achieved SBP 120-129 mmHg and 130-139 mmHg, had highest prevalence of MI (66%, 60%, 57%, p < 0.001), PCI (61%, 59%, 56%, p < 0.001), and HF admission (8%, 5%, 5%, p < 0.001). Furthermore, the left ventricular ejection fraction was lowest in this group (53%, 56%, 57%, p < 0.001). Similarly, those who had achieved a DBP < 60 mmHg comparing with those who achieved DBP 60-69 mmHg and 70-79 mmHg, were older (72 years, 69 years, 66 years, p < 0.001), and had highest prevalence of CABG (37%, 29%, 26%, p < 0.001), stroke (10%, 5%, 5%, p < 0.001), HF admission (13%, 6%, 5%, p < 0.001), and diabetes (43%, 40%, 34%, p < 0.001). Furthermore, the left ventricular ejection fraction was lowest in this group (51%, 55%, 56%, p < 0.001). This scenario was very similar to those in the post-hoc analysis of the INVEST trial.[46] In none of the retrospective analyses was it possible to control adequately for the many interacting co-morbid conditions.[47] A similar finding was observed in another large ARIC (Atherosclerosis Risk in Communities) cohort, in which DBP less than 60 mmHg was independently associated with higher blood levels of high-sensitivity cardiac troponin-T, more frequent coronary disease events, HF, and mortality, particularly when SBP exceeds 120 mmHg.[48] Again, there were imbalance of the confounders making it difficult to draw any conclusion.

Recommendation

- For patients with a history of CHD, the traditional office BP targets are < 130/80 mmHg. (COR I, LOE B)

BP TARGETS FOR PATIENTS WITH A HISTORY OF STROKE

Traditional office BP measurement

Patients with prior stroke were excluded in the SPRINT trial. This is because SPS3 trial has already been started, which investigated an SBP target of 130 mmHg vs. 150 mmHg in patients with a history of stroke.[49,50] The SPS3 trial failed to show a significant reduction in total stroke, which is the primary endpoint in the SPS3 trial, though intracerebral hemorrhage was reduced significantly.[50] The decision to treat hypertension in patients with a history of stroke still depends on the disease type and stage. The appropriate antihypertensive regimen and BP target in acute stroke remains controversial.

During the initial 30 hours in the acute stage of stroke, it is harmful to use angiotensin-receptor blocker

to decrease BP.[51] In the ENOS trial enrolling patients with an acute ischemic or hemorrhagic stroke and high SBP (140-220 mmHg), acute administration of transdermal glyceryl trinitrate (5 mg per day) within 48 h of stroke did not improve the functional status at 90 days, despite a significant BP lowering at day 1.[52] A subset of patients in this trial, who were taking antihypertensive drugs before their stroke, was also randomly assigned to continuing or stopping their medications. The results did not support continuing pre-stroke antihypertensive drugs in patients in the first few days after acute stroke.

In patients with acute hemorrhagic stroke, cumulating evidence indicated that early BP lowering could reduce hematoma expansion. Therefore, in patients with acute hemorrhagic stroke, a SBP > 180 mmHg can be decreased to < 140 mmHg. Recently, the ATACH-2 trial randomly assigned participants with intracerebral hemorrhage (volume < 60 cm^3) and a Glasgow Coma Scale score of 5 or more to a SBP target of 110 to 139 mmHg (intensive treatment) or a target of 140 to 179 mmHg (standard treatment).[53] The mean SBP at baseline was 200.6 ± 27.0 mmHg. Intravenous nicardipine was administered within 4.5 hours after symptom onset. Enrollment was stopped because of futility after a pre-specified interim analysis.

Recommendation

- For patients with a history of stroke, the traditional office BP targets are < 140/90 mmHg. (COR I, LOE A)

BP TARGETS FOR CKD

AOBP

Among the total 9,361 participants in the SPRINT trial, 2,646 (28.3%) had baseline eGFR between 20 and 60 ml/min/1.73 m^2. Intensive BP treatment to SBP < 120 mmHg led to a significant 25% reduction in the composite CV endpoints, compared with standard BP treatment to SBP < 140 mmHg. Subgroup analysis revealed the benefit also existed in the CKD group (18% reduction in hazard ratio), with a p value of interaction 0.32 between CKD and non-CKD patients, suggesting a beneficial effect across whole patient population. For CKD patients, there was a non-significant decrease in the composite renal endpoints (a 50% decline in eGFR from baseline, dialysis, or renal transplantation). However, in participants without CKD at baseline, the renal endpoint, defined as a decline ≥ 30% in eGFR to a value less than 60 ml/min/1.73 m^2, occurred more frequently in the intensive arm compared to the standard arm (HR 3.48, p < 0.001), though the absolute risk increase was only 0.86% per year.

The SPRINT is the largest CV outcome trial for CKD patients. The number of CKD patient in the SPRINT trial (n = 2,646) is more than the total combined patient number of the 3 CKD trials: MDRD (n = 840),[54] the African American Study of Kidney Disease and Hypertension (AASK) (n = 1,094),[55] and the Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2) trial (n = 338),[56] and is the first large-scaled target-driven CV outcome trial for CKD patients. Nevertheless, the results from the SPRINT trial cannot be extended to patients with heavy proteinuria (> 1 gm/day), diabetic nephropathy, polycystic kidneys, and eGFR < 20 ml/min/1.73 m^2 (MDRD).

The benefit of intensive BP control in CKD patients was supported by a recent meta-regression of 123 studies with 613,815 participants, in which SPRINT trial was included.[14] Relative risk reductions were found proportional to the magnitude of the achieved BP reductions, and a SBP < 130 mmHg is beneficial in individuals with a history of CVD, CHD, stroke, diabetes, HF, and CKD.[14] In the subgroup analysis, patients with baseline CKD had benefits from intensive BP control (RR 0.84, 95% CI 0.73-0.96), though patients without CKD benefit more (RR 0.68, 95% CI 0.62-0.75, p for interaction 0.0122).

Regarding chronic dialysis patients with hypertension, supporting evidence for antihypertensive pharmacotherapy is sparse. However, owing to an overdriven sympathetic nervous system in this population, β-blockers may be considered as the first-line therapy.[57]

Recommendation

- For patients with CKD with an eGFR of 20-60 ml/min/1.73 m^2, the AOBP target for SBP is < 120 mmHg. (COR I, LOE B)

Traditional office BP measurement

There has been no large scaled RCT for testing the effects of different office BP targets on CV outcomes in CKD patients in recent 2 years. Most of the previous

RCTs, using traditional office BP measurement in CKD patients were focused on renal outcomes, not CV outcomes, for different BP targets. In 3 trials enrolling non-diabetic patients with CKD, patients who were randomized to a target SBP of 125-130 mmHg had no significant difference in ESRD or all-cause death, compared with patients who were randomized to a target BP of < 140 mmHg.[54-56] Several meta-analyses did not support a target of < 130/80 mmHg.[58,59] A recent analysis from a nationwide cohort of US veterans with prevalent CKD, stricter SBP control to < 120 mmHg, compared to a target of 120-139 mmHg, was associated with higher all-cause mortality.[60] For patients with proteinuria, post-hoc analysis from the modification of diet in renal disease (MDRD) study indicated that the benefit of a lower BP target (< 130/80 mmHg) was limited to renal outcomes.[61] Therefore, we did not change the previous recommendations for traditional office BP targets in CKD patients.

Recommendations

- For patients with CKD stages 2-4 without albuminuria, BP targets are < 140/90 mmHg. (COR I, LOE A).
- In patients with CKD stages 2-4, but with albuminuria, BP targets are < 130/80 mmHg. (COR IIb, LOE C).

BP TARGETS FOR THE ELDERLY

The overall prevalence of hypertension among Taiwanese adults (≥ 20 years of age) is approximately 25%, and it increases to 58% in adults aged 65 years or older.[62] In keeping with the above observation, there is always a debate regarding whether the BP target for the elderly should be the same as or looser than that for the younger hypertensive patients, as recommended by the 2014 JNC report.[8] This controversy becomes even more confused as the most recently released hypertension management guideline of the American College of Physicians and the American Academy of Family Physicians still suggested that, in adults aged 60 years or older, the treatment target remains SBP less than 150 mmHg, rather than 140 mmHg.[63]

In this focused update, we reviewed all RCTs and meta-analyses regarding hypertension management in older adults, particularly those done in East Asian populations, and made our recommendations for BP targets in elderly hypertensive patients. The definition of "elderly" adopted here is age ≥ 75 years due to 1) with the life expectancy of over 80 years in Taiwan, age of 75 years (middle-old), rather than 65 years (young-old), is chronologically more appropriate to define elderly, 2) this definition has been adopted in other Asian (Japan) hypertension guideline,[64] which has similar ethnic and social backgrounds to Taiwan, and 3) this definition has been adopted in landmark hypertension trials like SPRINT, the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS), and the valsartan in elderly isolated systolic hypertension (VALISH) study, etc.[5,6,65]

AOBP

The SPRINT trial has unequivocally demonstrated that targeting a SBP of less than 120 mmHg, compared to less than 140 mmHg, resulting in a significant 25% reduction in fatal and non-fatal CV events and a 27% reduction in all-cause mortality.[4] The pre-specified subgroup analysis in elderly (≥ 75 years) SPRINT patients was also published.[65] Among the 2,636 ambulatory elderly participants (mean age, 79.9 years; 37.9% women; baseline SBP 142 mmHg) with a median follow-up of 3.14 years, targeting an SBP of less than 120 mmHg, as compared with less than 140 mmHg, achieved a significant 34% reduction in fatal and non-fatal CV events and a 33% reduction in all-cause mortality.[65] The effects of aggressive BP lowering were irrespective of the frailty and ambulatory capacity of participants. The overall rate of serious adverse events was not different between treatment groups (48% in both groups). Absolute rates of hypotension were 2.4% in the intensive treatment group vs. 1.4% in the standard treatment group, 3.0% vs. 2.4% for syncope, and 4.9% vs. 5.5% for injurious falls. Instead of directly embracing the SPRINT results, several issues remain. First, the BP measurement adopted in the SPRINT trial, the unattended AOBP, is different from the BP measurements used in most RCTs. This BP measurement can effectively eradicate the impact of white-coat effect, and has been reported to be lower than conventional office BP at approximately 16/7 mmHg.[21,22] Since the accuracy of BP measurement is of vital importance, we therefore recommend the SBP target of less than 120 mmHg for elderly hypertensive pa-

tients if unattended AOBP can be used. The intentions are two-folds: one is to eradicate the myth that BP reduction should be conservative in elderly patients, and second is to promote the application of unattended AOBP in clinical practice. Second, patients with orthostatic hypotension, diabetes, and prior stroke were excluded from the SPRINT trial. However, it has been shown that there was no significant heterogeneity in results between the SPRINT and the ACCORD trial, which included exclusively diabetic patients and using the same study design as in the SPRINT trial.[34] The findings in the HOPE-3 trial seem to be in the different direction,[33] in which patients with baseline SBP of ≤ 131.5 mmHg was associated with numerically higher major CV events. Though the HOPE-3 trial included 3,691 Chinese patients out of 12,705 participants with a mean baseline BP of 138/82 mmHg, one should be aware that the HOPE-3 trial is a primary prevention trial with a 10-year CV risk of only 8%, much lower than that in the SPRINT trial (above 20% overall and above 25% in aged ≥ 75 years). It is noteworthy that patients with East Asian ethnicity in the SPRINT trial are very few (< 2%).

Recommendation

- For elderly patients with an age ≥ 75 years, the AOBP target for SBP is < 120 mmHg. (COR I, LOE B).

Traditional office BP measurement

In a meta-analysis including 31 trials and 190,606 participants, there were no differences between younger (< 65 years) and older (≥ 65 years) adults in the effects of lowering BP on major CV events.[66] In the FEVER trial, which included 9,711 Chinese stages 1 and 2 hypertensive patients, effects of lowering BP were significantly greater in older (> 65 years) patients, compared to younger (≤ 65 years) patients, in terms of relative risk reductions.[31] With the age cut-off of 75 years, the ADVANCE, VALISH, and SPRINT trials all showed no differences between patients < 75 years and those ≥ 75 years in the effects of lowering BP on major CV events.[4,6,67] However, in the JATOS trial, which included 4,418 Japanese stages 2 and 3 hypertensive patients aged ≥ 65 years, effects of BP lowering were significantly smaller in patients ≥ 75 years with regard to cerebrovascular events.[5] This finding reminds us that vigilance is required in managing elderly patients with higher baseline BP (e.g., SBP > 160 mmHg).

Most of the hypertension trials enrolling patients older than 60 or 65 are associated with achieved systolic BP > 140 mmHg. In a recent meta-analysis including 4 high-quality trials involving 10,857 older (≥ 65 years) hypertensive patients with a mean follow-up of 3.1 years and achieved SBP of < 140 mmHg,[5,6,65,68] intensive BP lowering (SBP < 140 mmHg) was associated with a 29% reduction in major CV event, 33% reduction in CV mortality, and 37% reduction in HF (RR: 0.63; 95% CI: 0.43 to 0.99), compared with standard BP lowering (SBP ≥ 140 mmHg except SPRINT-SENIOR).[16,68] There was no significant difference in the incidence of serious adverse events or renal failure between the 2 groups. Among the 4 trials, 3 trials comprising a total of 7,921 patients with an average age of 76 years were from East Asia.[5,6,68]

Recommendation

- For elderly patients with an age ≥ 75 years, BP targets, using traditional BP measurement, are < 140/90 mmHg. (COR I, LOE B)

To avoid the untoward effects of too aggressive BP reduction in the elderly, we suggest the followings. First, check standing BP for the possibility of orthostatic hypotension in every elderly hypertensive patient at baseline, monthly, and after adjustment of medications. Second, clinicians should ensure that accurate measurement of BP before starting or changing treatment of hypertension. Assessment may include multiple measurements in clinical settings (for example, 2 to 3 readings separated by 1 minute in a seated patient who is resting alone in a room) or home or ambulatory monitoring. Third, BP should be reduced gradually and cautiously in elderly patients. If not at goal, antihypertensive drug treatment should be adjusted at an interval of 1 to 3 months and re-evaluated. Signs of brain ischemia, such as dizziness and orthostatic dizziness, the presence of carotid bruits, symptoms of angina pectoris, and ECG changes should be carefully evaluated.

CONCLUSIONS

After so many years of confusion regarding optimal BP targets and query about J curve phenomenon, it has become clearer that intensive BP strategy will benefit a

large proportion of hypertensive patients. For secondary prevention, the SPRINT trial has provided compelling evidence to support an SBP target of < 120 mmHg, using AOBP, for elderly patients with age ≥ 75 years, for patients with CHD, and for patients with CKD with an eGFR 20-60 ml/min/1.73 m^2. For diabetic patients, it is reasonable to decrease office BP to < 130/80 mmHg. We are still waiting for the European Society of Hypertension and Chinese Hypertension League Stroke in Hypertension Optimal Treatment (ESH-CHL-SHOT) trial to answer the optimal BP targets for patients with a history of stroke.[69] When applying the intensive SBP target of < 120 mmHg, one should always rely on AOBP measurement, though HBPM could possibly be a surrogate for AOBP.

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CONFLICTS OF INTEREST

Chern-En Chiang has been on the speaker bureau for Astrazeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, GSK, MSD, Novartis, Pfizer, Roche, Sanofi, Servier, Tanabe, Takeda, and TTY.

Tzung-Dau Wang has been on the speakers bureau for Abbott, AstraZeneca, Bayer, Biosensor, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, MSD, Novartis, Pfizer, and Sanofi.

Tsung-Hsien Lin has no conflict of interest.

Hung-I Yeh has been on the speakers bureau for AstraZeneca, Daiichi-Sankyo, GSK, MSD, Pfizer, Tanabe, and Takeda.

Ping-Yen Liu has no conflict of interest.

Hao-Min Cheng has no conflict of interest.

Ting-Hsing Chao has been on speaker's bureau of Abbott Laboratories, AstraZeneca Pharmaceuticals, Bayer Healthcare Pharmaceuticals, Boehringer-Ingelheim, Daiichi Sankyo, Pfizer, Merck & Co., Inc., Novartis Corporation, Otsuka Pharmaceutical Co., Sanofi-Aventis.

Chen-Huan Chen has no conflict of interest.

Kou-Gi Shyu has no conflict of interest.

Kwo-Chang Ueng has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, GSK, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, Servier, Tanabe, Takeda, and TTY.

Chung-Yin Chen has no conflict of interest.

Pao-Hsien Chu has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, GSK, MSD, Novartis, Pfizer, Roche, Sanofi, Servier, Tanabe, and Takeda.

Shih-Hsien Sung has no conflict of interest.

Kang-Ling Wang received honorarium from AstraZeneca, Bayer, Boehringer Ingelheim, and Daiichi-Sankyo.

Yi-Heng Li has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Pfizer, Amgen and Sanofi.

Kuo-Yang Wang has no conflict of interest.

Fu-Tien Chiang has no conflict of interest.

Wen-Ter Lai has no conflict of interest.

Jyh-Hong Chen has no conflict of interest.

Wen-Jone Chen has no conflict of interest.

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